RLL-170US

17/ Req for Recons

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant: RAMPAL *et al.*

Examiner: Micah Paul Young

Application No.: 09/941,970

Group Art Unit: 1615

Filing Date: August 29, 2001

Bet 6-26-03

Title: **CONTROLLED RELEASE FORMULATION OF ERYTHROMYCIN OR A DERIVATIVE THEREOF**

Certificate of Facsimile

I certify that this correspondence is sent by facsimile on June 24, 2003 to the United States Postal Service under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Kim Campbell

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Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION DATED MARCH 14, 2003

Initially, Applicants wish to express their appreciation to the Examiner for the telephone interview on June 23, 2003 in which the Examiner withdrew the double patenting rejection for conflicting claims.

In view of the following remarks, reconsideration and allowance of this application are requested. Claims 1, 2, and 5-12 are pending with claims 1, 11, and 12 being independent.

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I. Double Patenting Rejection

Claims 1, 2, 9, and 11 are rejected for double patenting over claims 1-7, 18, 19, and 22 of U.S. Patent Application No. 10/054,077. During a telephone interview on June 23, 2003, the Examiner withdrew this rejection.

II. Rejection for Double Patenting Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1, 2, 9, and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 18, 19, and 22 of co-pending U.S. Patent Application No. 10/054,077. Applicants respectfully submit that because neither Claims 1, 2, 9, and 11 of this application nor claims 1-7, 18, 19, and 22 of co-pending U.S. Patent Application No. 10/054,077 have been allowed, Applicants will evaluate whether a terminal disclaimer is appropriate when either set of claims is allowed and the rejection is no longer provisional.

Claims 1, 2, and 5-12 have been rejected as being obvious over Talwar (WO 00/15198) in view of either of Fuisz (U.S. Patent No. 5,518,730), Ayer (U.S. Patent No. 6,096,339), or Misra (U.S. Patent No. 5,869,098).

III. Rejection under 35 U.S.C. § 103(a) over Talwar (WO 00/15198) in view of Fuisz (U.S. Patent No. 5,518,730)

Claim 1 is directed to a controlled release formulation of erythromycin A or a derivative thereof and pharmaceutically acceptable rate controlling polymers that are suitable for once daily administration. The formulation includes erythromycin from about 66% w/w to about 90% w/w of the total tablet weight and the pharmaceutically acceptable rate controlling polymers from 0.1% w/w to about 4% w/w of the total tablet weight.

Talwar discloses controlled release dosage forms that include an active ingredient, a gas generating component, a swelling agent, a viscolyzing agent, and gelling polymers and provide a combination of temporal and spatial (e.g., particular portion of the gastrointestinal tract) control over drug delivery. Talwar also discloses formulations of

the antibiotic ciprofloxacin. See e.g., Examples 1-3, 10, and 11. The antibiotic is present in a concentration of between 55.16% and 71.43% w/w of the tablet and the polymer is present in a concentration of between 1.02% and 1.84% w/w. The total tablet weight and antibiotic in the tablet in Examples 1-3, 10, and 11 are 1085 mg and 598.47 mg; 1400 mg and 1000 mg; 975 mg and 600 mg; 701.99 mg and 599.99 mg; and 1140 mg and 1000 mg, respectfully. Talwar's formulations further include polyvinyl pyrrolidone, magnesium stearate and talc. However, the Office Action states that Talwar does not disclose erythromycin as the pharmaceutically active agent and relies on Fuisz to supply erythromycin.

Fuisz discloses a controlled release formulation in which erythromycin is listed as one possible bio-effective agent in a list containing over thirty classes of agents and over one hundred individual bio-active agents. See Col. 7, line 27 through col. 9, line 8. Fuisz's formulation is structured to extend the bio-effective agent's release for two weeks. See Table 2; Col. 13, lines 10-30. The formulation also includes rate-controlling polymers, such as hydroxypropylmethylcellulose at a concentration level of 50 to 99% w/w. See Col. 11, line 19. The Office Action asserts that it would have been obvious for one skilled in the art to have modified Talwar in view of Fuisz to include Fuisz's erythromycin in place of ciprofloxacin. According to the Office Action, erythromycin is "a different yet equally effective antibiotic agent" as ciprofloxacin, they "are well known antibiotics," and "[s]ubstituting and interchanging is well within the level of ordinary skill in the art."

Applicants respectfully disagree because neither Talwar nor Fuisz presents a suggestion or motivation for one skilled in the art to modify Talwar to include Fuisz's erythromycin because they employ completely different formulations and dose controlling strategies. As described above, the teachings of Talwar are directed to a once daily formulation employing a controlled gastric release of the active ingredient. In contrast, Fuisz employs a sustained release formulation lasting up to two weeks. In disclosing his formulation, Talwar inherently teaches away from such sustained release formulations and high concentrations of rate-releasing polymers as relied upon in Fuisz, which contains between 55 to 99 % w/w polymer concentration. See Col. 11, line 19. Thus, one of skill in the art would not have been motivated to use Fuisz's disclosures of a

two week sustained release formulation to modify Talwar's twenty four hour controlled release formulation.

Moreover, the Office Action characterizes erythromycin and ciprofloxacin as "different yet equally effective * * * and substituting these compounds is well within the level of ordinary skill in the art." However, Applicants submit that these drugs are not swappable or interchangeable, and thus one skilled in the art would not have been motivated to combine these references. Ciprofloxacin is classified as a fluoroquinolone, which inhibits bacterial gyrase, resulting in inhibition of DNA replication and ultimately ending the infection. This family of antibiotics has developed marked resistance to gram-positive organisms, and consequently their utility remains to treatment of gram-negative infections. Further, ciprofloxacin is stable in gastric acids and is absorbed almost entirely in the region extending from the stomach to the jejunum[1].

In contrast, erythromycin and its derivates (i.e., clarithromycin) belong to the macrolide family of antibiotics. Different from fluoroquinolones, macrolide agents function by inhibiting RNA-dependent protein synthesis, and not acting on DNA replication directly. Also, in contrast to fluoroquinolones, macrolides utility is in fighting gram-positive bacteria, and variably gram-negative bacteria. Further, the absorption of, for example, clarithromycin occurs in the upper region of the small intestine in which the pH is approximately 5.0. Although broadly classified as antibiotics, they both maintain separate and distinct utilities, modes of action, and regions of absorption. As such, Applicants hold that one skilled in the art would not have viewed ciprofloxacin and erythromycin (and its derivates) as equally effective and interchangeable as asserted in the Office Action. For at least the reasons described above, claims 1, 2, and 5-10 are allowable over Talwar and Fuisz, taken separately or in combination.

Claim 12, like claim 1, recites a controlled release formulation of erythromycin A or a derivative thereof suitable for once daily administration in an amount from about 66% w/w to about 90% w/w of the total tablet weight with about 0.1% to about 4% w/w of one or more pharmaceutically acceptable rate controlling polymers. Accordingly,

[1] The spatial arrangement of the gastrointestinal system is as follows: stomach, duodenum, jejunum, ileum, colon, rectum, and anus. The duodenum, jejunum, and ileum make up the small intestine.

claim 12 is allowable over Talwar and Fuisz, taken separately or in combination, for the same reasons that claim 1 is allowable.

Claim 11 is directed to a monolithic controlled release formulation of clarithromycin comprising 1000 mg of clarithromycin. The total weight of the dosage unit is not more than 1500 mg.

As stated above, claim 11 is rejected as being obvious over the combination of Talwar and Fuisz. Claim 11 is directed to a monolithic controlled release formulation of clarithromycin comprising 1000 mg of clarithromycin. The total weight of the dosage unit is not more than 1500 mg.

Fuisz does not disclose the weights of his formulations much less any formulation that includes erythromycin. Talwar discloses a 1400 mg tablet having 1000 mg of ciprofloxacin (See Example 2). Nonetheless, for the reasons described above, there would have been no motivation to combine Talwar and Fuisz as suggested in the Office Action and, accordingly, claim 11 is allowable over Talwar and Fuisz, taken separately or in combination.

IV. Rejection under 35 U.S.C. § 103(a) over Talwar (WO 00/15198) in view of Ayer (U.S. Patent No. 6,096,339)

Ayer describes a controlled release formulation in which erythromycin is disclosed as a possible bio-effective agent in the form of a tablet produced by granulation. See Example 4; Col. 11, lines 65-67. Ayer's various tablets are described as functioning by leaching, osmosis, hydrokinetics, push displacement, erosion, and dissolution. Ayer discloses that antibiotics, among a large number of other bio-effective agents, can be used in his tablets. See Col. 11, line 48 through Col. 12, line 36. Ayer later discloses that erythromycin can be used in his tablets. Ayer also states that the bio-effective agent can be combined with rate controlling, hydrophilic water soluble polymers such as cellulose derivatives. See Col. 12, lines 10-15.

The Office Action asserts that it would have been obvious to one skilled in the art to modify Talwar in view of Ayer to use Ayer's erythromycin in place of Talwar's ciprofloxacin. Applicants respectfully disagree because neither Talwar nor Ayer, taken

separately or in combination, provides a motivation to modify Talwar in the manner asserted in the Office Action. Moreover, because of the large number of classes of bio-effective agents disclosed in Ayer, and the even larger number of specific agents disclosed in Ayer, it would have required undue experimentation to come up with the particular combination proposed in the Office Action. Because of the undue experimentation necessary to form that combination, and the lack of motivation in the references, Applicants respectfully submit that such a combination is possible only through the application of impermissible hindsight reconstruction. Finally, the Office Action characterizes erythromycin and ciprofloxacin as "different yet equally effective" and that "substituting these compounds is well within the level of ordinary skill in the art." However, Applicants submit that these drugs are not swappable or interchangeable, and for this additional reason one skilled in the art would not have been motivated to combine these references.

Talwar describes the prior art methods of controlled delivery of drugs, their various limitations, and concludes that none of them are completely satisfactory. For example, Talwar describes granules and tablets as not providing the desired spatial control. See Page 5. As stated above, Ayer provides tablets that are formed from granules and function by leaching, osmosis, hydrokinetics, push displacement, erosion, or dissolution, some of which are generally those prior art methods disclosed by Talwar as not being completely satisfactory. As such, Talwar denigrates the methods disclosed in Ayer and one of ordinary skill in the art would not have been motivated to look to Ayer to modify Talwar.

Arguendo, if there had been some source of motivation to look at Ayer to modify Talwar, one of ordinary skill in the art would have had to engage in undue experimentation to select the combination asserted in the Office Action. Specifically, Talwar discloses five broad classes of drug and Ayer discloses at least thirty broad classes of drugs and over one hundred specific drugs. With Talwar and Ayer providing such large lists of possible drug classes and drugs, the Office Action is essentially asserting that one of ordinary skill in the art would have selected Talwar's ciprofloxacin examples (examples 3 and 4) from Talwar's twelve examples and then selected erythromycin from Ayer list of over one hundred specific drugs to create the combination

asserted in the Office Action. Without some motivation in either Talwar or Ayer to select that specific combination, one of ordinary skill in the art would have had to engage in an undue amount of experimentation to make the selection asserted in the Office Action. Alternatively, such a combination is apparent only through hindsight reconstruction by using the rejected claims as a guide to both selecting the necessary elements from Talwar and Ayer, and combining them to form the asserted combination.

Further, the Office Action characterizes erythromycin and ciprofloxacin as "different yet equally effective * * * and substituting these compounds is well within the level of ordinary skill in the art." However, Applicants submit that these drugs are not swappable or interchangeable, and thus one skilled in the art would not have been motivated to combine these references. As described above, ciprofloxacin is classified as a fluoroquinolone, which inhibits bacterial gyrase, resulting in inhibition of DNA replication and ultimately ending the infection. This family of antibiotics has developed marked resistance to gram-positive organisms, and therefore their utility is left to gram-negative infections. Finally, ciprofloxacin is stable in gastric acids and is absorbed almost entirely in the region extending from the stomach to the jejunum. In contrast, erythromycin and its derivates (i.e., clarithromycin) belong to the macrolide family of antibiotics and function by inhibiting RNA-dependent protein synthesis, and not by acting on DNA replication directly. Also, in contrast to fluoroquinolones, macrolides utility is in fighting gram-positive bacteria, and variably gram-negative bacteria. Finally, the absorption of, for example, clarithromycin occurs in the upper region of the small intestine in which the pH is approximately 5.0. Although broadly classified as antibiotics, they both maintain separate and distinct utilities, modes of action, and regions of absorption. Again, Applicants hold that one skilled in the art would not view ciprofloxacin and erythromycin (and derivates) as equally effective and interchangeable. For the reasons described above, claim 1 and dependent claims 2 and 5-10 are allowable over Talwar and Ayer, taken separately or in combination.

Claim 12, like claim 1, recites a controlled release formulation of erythromycin A or a derivative thereof suitable for once daily administration in an amount from about 66% w/w to about 90% w/w of the total tablet weight with about 0.1% to about 4% w/w of one or more pharmaceutically acceptable rate controlling polymers. Accordingly,

claim 12 is allowable over Talwar and Ayer, taken separately or in combination, for the same reasons that claim 1 is allowable.

Claim 11 is directed to a monolithic controlled release formulation of clarithromycin comprising 1000 mg of clarithromycin. The total weight of the dosage unit is not more than 1500 mg.

Ayer states that his dosage forms can have between 0.05 nanograms and 1.2 grams of a drug having a particular particle size range. Ciprofloxacin is disclosed as being present in a dosage form at 500 mg. Talwar discloses a 1400 mg tablet having 1000 mg of ciprofloxacin (See Example 2). Nonetheless, for the reasons described above, there would have been no motivation to combine Talwar and Ayer as suggested in the Office Action and, accordingly, claim 11 is allowable over Talwar and Ayer, taken separately or in combination.

V. Rejection under 35 U.S.C. § 103(a) over Talwar (WO 00/15198) in view of Misra (U.S. Patent No. 5,869,098)

Misra discloses a fast dissolving formulation utilizing various bio-effective agents and that rapidly dissolves in the mouth with a dissolution time in the range of from about 3 to 30 seconds. See Co . 2, line 46-49. Misra discloses over seventy five different classes of drugs from which the bio-active agent can be selected. See Col. 8, line 53 through Col. 10, line 29; Col.12, lines 35-38. The Office Action asserts that it would have been obvious for one of skill in the art to have modified Talwar in view of Misra to include Misra's clarithromycin. Applicants respectfully disagree because neither Talwar nor Misra presents a suggestion or motivation for one skilled in the art to modify Talwar to include Misra's clarithromycin. Instead, one skilled in the art would not seek to combine Misra and Talwar because they employ completely different formulations and dose controlling strategies. As described above, the teachings of Talwar are directed to a once daily formulation employing a controlled gastric release of the active ingredient. In contrast, Misra teaches a fast orally dissolving formulation. One of skill in the art would not have looked to a fast orally dissolving formulation to modify a controlled release tablet that delivers the drug in a particular spatial portion of the gastrointestinal tract because such delivery locations are completely different and have different properties.

Further, Misra's vague reference to clarithromycin in an extensive list of bio-active agents does not automatically suggest to one skilled in the art that clarithromycin is "a different yet equally effective antibiotic agent" that can be swapped with ciprofloxacin. Applicants submit that these drugs are not swappable or interchangeable for the reasons described in detail above.

For at least the reasons described above, claims 1, 2, and 5-10 are allowed over Talwar and Misra, taken separately or in combination.

Claim 12, like claim 1, recites a controlled release formulation of erythromycin A or a derivative thereof suitable for once daily administration in an amount from about 66% w/w to about 90% w/w of the total tablet weight with about 0.1% to about 4% w/w of one or more pharmaceutically acceptable rate controlling polymers. Accordingly, claim 12 is allowable over Talwar and Misra, taken separately or in combination, for the same reasons that claim 1 is allowable.

Claim 11 is directed to a monolithic controlled release formulation of clarithromycin comprising 1000 mg of clarithromycin. The total weight of the dosage unit is not more than 1500 mg.

Misra discloses tablets having weights of 500 mg, 650 mg, and 750 mg. Talwar discloses a 1400 mg tablet having 1000 mg of ciprofloxacin (See Example 2). Nonetheless, for the reasons described above, there would have been no motivation to combine Talwar and Misra as suggested in the Office Action and, accordingly, claim 11 is allowable over Talwar and Misra, taken separately or in combination.

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Conclusion

For the reasons stated above, the Examiner is urged to pass claims 1, 2, and 5-12 to issue. Authorization is hereby given to charge any fees deemed to be due in connection with this Response to Office Action to Deposit Account No. 50-0912.

Respectfully submitted,

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Date: June 24, 2003

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FROM: Kim Campbell, IP Dept.

RE: Response to Office Action
PATENT APPLN. NO. 09/941,970
FILING DATE: August 29, 2001
Our Reference No.: RLL-170US

Please find attached the Petition for Extension of Time Under 37 CFR 1.136 (a) and Response to Office Action dated March 14, 2003.

Sincerely,

Kim Campbell
Patent Legal Assistant